REMARKS

Claims 1, 3-10, and 12-15 are pending. Claims 2, 11, and 16-19 are canceled. The listing of claims is presented as a matter of convenience. No amendments are made in this paper. No new matter is entered.

Applicants reserve the right to pursue one or more continuing applications to any canceled subject matter.

Information Disclosure Statement

Applicants respectfully request consideration of the supplemental Information Disclosure Statement submitted December 3, 2008 (see USPTO Image File Wrapper). Applicants are entitled to the consideration of the IDS as a matter of right in view of the RCE filed January 15, 2009. As such, Applicants respectfully request return of an initialed copy of the Form SB08a submitted December 3, 2008.

In addition, Applicants respectfully request consideration of the supplemental IDS submitted herewith.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3-10, and 12-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Takahashi et al (WO 02/36135, herein referred to as "WO '135") in view of van Kesteren et al. (Clinical Cancer Research, vol. 6, p. 4725, 2000, herein referred to as "van Kesteren"), Takahashi et al. (Clinical Cancer Research, vol. 7, p. 3251, 2001, herein referred to as "Takahashi 2001"), and Dorr et al. (Cancer Chemotherapy Handbook, 2nd ed., p. 395, 1994, herein referred to as "Dorr").

The Office Action asserts that WO '135 teaches the method of combination therapy of ET-743 and doxorubicin to treat sarcoma in a human, and that one of ordinary skill in the art would have looked to van Kesteren for dosage information for ET-743 administered as an i.v. infusion every 3 weeks to a human patient to treat the cancer sarcoma, and to Takahashi 2001 for the treatment protocol of ET-743 and doxorubicin administered at a constant molar ratio of 1:100 ET-743:doxorubicin concomitantly to treat sarcoma cells. According to the Office Action, one of ordinary skill in the art would have a reasonable expectation of success in combining WO '135 with the dosage taught by van Kesteren and the ratio taught by Takahashi 2001 because van Kesteren teaches that the particular ET-743 dosage is safe in a human, and Dorr teaches that a dosage of doxorubicin of 60-75 mg/m^2 with administration every 3 weeks is safe in a human. Thus, by the reasoning of the Office Action, it would have been routine experimentation for one skilled in the art at the time of the invention to optimize the dosage of the compounds.

As a point of clarification, where the Office Action comments on "Applicant's remarks regarding the *antagonistic effects* between doxorubicin and other agents," Applicants wish to point out that there is a distinction between "antagonistic effects" and "adverse effects" in this field. Applicants' previous comments provided in the response filed on January 15, 2009, were directed to the risk of the appearance of adverse effects when combining two anticancer drugs in the clinical setting and the difficulty in finding suitable clinical dosages for the combination. Applicants provided evidence to support the idea of adverse effects with several examples from the literature showing adverse effects are encountered when administering a combination of doxorubicin with certain drugs to human patients.

van Kesteren

The Office Action states that "Van Kesteren et al. teaches ET-743 administered at the specific dosage 600 mcg/m^2, or 0.6 mg/m^2, administered every 21 days during multiple courses (page 4728, right column, section RESULTS)" (see Office Action, p. 5, lines 12-14). This is not an accurate summary of the reference as van Kesteren actually teaches an infusion dose of 1500 mcg/m^2. This higher dosage value was identified as the Recommended Dose (RD) for Phase II studies (see van Kesteren, Abstract, pages 4728-4730, Results Section, and discussion on page 4730). Accordingly, the dosage of 1500 mcg/m^2 (1.5 mg/m^2) of ET-743 taught by van Kesteren would not lead one of ordinary skill in the art to the claimed dose of "between 0.6 and 0.75 mg/m^2 for ET-743".

Moreover, a dose of 600 mcg/m^2 was only one of the dosages administered during the dose-finding study of van Kesteren. In particular, a dosage of 600 mcg/m^2 of ET-743 was administered as single agent in human patients but not in a combination therapy, let alone when in combination with doxorubicin. The reference clearly teaches away from a dose of 600 mcg/m^2 in that the reference recommends a dose of 1500 mcg/m^2 (1.5 mg/m^2) of ET-743 as being the most efficacious safe dose. On the other hand, based on the clinical Phase I data provided in the present specification, the combination of ET-743 in a dose range of 0.6 to 0.75 mg/m^2 with doxorubicin in a dose of about 50 mg/m^2 or 60 mg/m^2 results in antitumor activity without dose-limiting toxicity.

The Office Action argues that van Kesteren teaches in the paragraph bridging 4731-32 that it is known in the art that the dosage for a human in terms of mcg/m^2 or mg/m^2 can be safely applied at higher dosages than in the mouse model (see Office Action, page 5, lines 14-16). Again, this is not an accurate summary of van Kesteren. In the context of the technical field of

preclinical toxicity studies, one of ordinary skill in the art understands that the primary aims of preclinical toxicity studies are to establish the maximal tolerated dose (MTD) in mice that will be used to estimate a baseline starting dose in Phase I trials in humans, and to identify effects on vital functions and target organ toxicity in relation to drug exposure and treatment cycles. Moreover, the establishment of the MTD and the dose-limiting toxicities in humans would be the primary end point of Phase I clinical trials. Thus, one of ordinary skill in the art would not make an assumption for the MTD in human patients based on data obtained in animal models in a preclinical stage.

The distinction and purpose of pre-clinical trials in mice and Phase I trials in humans is a point that is repeatedly misunderstood, as the Office Action again confuses the point later on in connection with Meco et al. (Cancer Chemother Pharmacol 2003, 52, p131-138, herein referred to as "Meco"). To clarify, Applicants provide in the attached IDS the following references: (i) the "Nonclinical Evaluation for Anticancer Pharmaceuticals" draft guidance from the FDA, and (ii) Newell et al. (European Journal of Cancer 40, 899-906, 2004; herein referred to as "Newell"). As taught by Newell, "the primary role of pre-clinical toxicology is to identify a safe Phase I trial starting dose, potential toxicities and their reversibility" (Newell, page 899, right column, lines 10-12, submitted in the attached IDS).

According to van Kesteren in the paragraph linking page 4731-32, "the starting dose in this Phase I study was 50 mcg/m^2, which was approximately one-tenth (1/10) of the LD10 (or MTD) found in mice (200 mcg/kg or 600 mcg/m^2)," where the LD10 is understood as the lethal dose for 10% of the mice.[1] Accordingly, the preclinical data in mice is used to establish a starting dose for the Phase I clinical trial which is described in van Kesteren. In the Phase I trial

[1] Please note that the conversion factor from mg/kg to mg/m^2 is different depending on the species. The factor used in mice to convert dosages expressed as mg/kg to mg/m^2 is 3 (200 mg/kg or 600 mg/m^2).

described by van Kesteren, several dose levels were evaluated and, as a result of the dosage escalation study, the MTD (1800 mcg/m^2) and the Dose Limiting Toxicities (DLT's) were identified and a Recommended Dose for Phase II studies was chosen (1500 mcg/m^2).

Thus, contrary to the arguments in the Office Action, there is nothing in the disclosure of van Kesteren that would lead a person skilled in the art to conclude that "the dosage for a human in terms of mcg/m^2 or mg/m^2 can be safely applied at higher dosages than in the mouse model" and indeed, such a conclusion is inconsistent with the protocols in the art.

Takahashi 2001

The Office Action further argues that Takahashi 2001 teaches that exposure of sarcoma cell lines to ET-743 and doxorubicin at a constant molar ratio of 1 ET-743: 100 doxorubicin resulted in synergistic interactions. According to the Office Action, the results shown in Takahashi 2001 teach a specific ratio of ET-743 and doxorubicin for a combination that does not result in antagonistic effects.

Takahashi 2001 describes *in vitro* studies examining the cytotoxocity resulting from combining ET-743 together with various other antineoplastic agents, including doxorubicin. It describes synergism between ET-743 and doxorubicin upon concurrent exposure in sarcoma cell lines. However, the cell line assays of Takahashi 2001 do not provide data for the effects of the combination of ET-743 and doxorubicin in a living organism. In particular, Takahashi 2001 does not provide data for the potential metabolic interactions of the drugs or about specific organ toxicities of the combined therapy. Thus, from the disclosure in Takahashi 2001, it is not possible to make conclusions on the toxicological interactions between ET-743 and doxorubicin in an *in vivo* setting at the assayed ratio.

Meco and Takahashi 2001

The Office Action cites Meco et al. (Cancer Chemother Pharmacol 2003, 52, p131-138, herein referred to as "Meco") as teaching the following:

> "[I]t is known in the art that the ratio of ET-743 to doxorubicin at a constant molar ratio of 1 ET-743: 100 doxorubicin is more effective than each drug given alone (page 134, left column, section In vivo studies), or is advantageously additive and safely tolerated by the mouse model."

(Office Action, page 8, lines 7-10). The argument appears to be based on a 1 ET-743: 100 doxorubicin ratio reported to be synergistically cytotoxic in the *in vitro* experiments disclosed in Takahashi 2001. The Office Action argues that the synergistic cytotoxicity was maintained in the *in vivo* assays shown in Meco. Accordingly, it is our understanding that with the expression "a constant molar ratio of 1 ET-743: 100 doxorubicin" the Examiner is referring to the fact that the combination of ET-743 and doxorubicin in the *in vivo* studies described in Meco is carried out at the doses of 0.1 mg/kg and 10 mg/kg, respectively, wherein effectively a ratio of 1:100 is maintained. However, this ratio is obtained from the dosages of the anticancer drugs which are administered to the animal model but not from the concentration levels (i.e., "molar ratio") of the anticancer drugs in the animal blood or tissues. Furthermore, the fact that the ratio described in Takahashi 2001 is repeated at the dosage level is just a coincidence because, as described in Meco (page 134, left column, "In vivo studies"), the dosages used in the combination were based on the optimal doses of ET-743 and doxorubicin given alone.

In the *in vivo* setting, the mean drug concentration is determined in plasma and in various tissues of the body, including tumours, as a function of time after administration. A person skilled in the art wishing to determine the drug exposure of ET-743 and doxorubicin in the *in vivo* assays shown in Meco would look to pharmacokinetic values such as, for example, the plasma levels of the drugs (see Figures 3a and 3b) and the AUC values. The AUC of doxorubicin

in mice treated with 10 mg/kg is around 2 mcg/ml.h, whereas the AUC of ET-743 found in mice is around 10 mcg/ml.h (see Meco, page 137, left column, lines 47-54). Accordingly, in the *in vivo* experiments described in Meco, the concentration ratio between the two drugs obtained from their plasma levels is 5:1 for ET-473 to doxorubicin.

Meco and van Kesteren

The Office Action continues to argue that van Kesteren teaches it is known in the art that the dosage for a human in terms of mcg/m^2 or mg/m^2 can be safely applied at higher dosages than in the mouse model (van Kesteren, page 4731, right column, paragraph 4 at bottom and page 4732, left column, paragraph 1 at top), specifically comparing the 200 mc/kg toxicity level in the mouse model in Meco (page 134, left column, "In vivo studies").

However, the art teaches away from this position, where "the primary role of pre-clinical toxicology is to identify a safe Phase I trial starting dose, potential toxicities and their reversibility" (Newell, page 899, right column, lines 10-12, submitted in the attached IDS). Although there is wide agreement in the art for the general aims for the design of preclinical toxicology studies, there is currently no consensus in the drug development community to "how many species should be used in the preclinical studies" and "how closely should this species be related to humans" (see for example, the section titled "Start dose for first administration in human" and "Note 2" of the "Nonclinical Evaluation for Anticancer Pharmaceuticals" draft guidance from the FDA, submitted herewith). Accordingly, Newell addresses the issue of establishing if preclinical toxicology studies in non-rodent species are routinely needed for the identification of a safe Phase I trial starting dose for human trials. Therefore, the aim of preclinical toxicology studies is to determine the safe starting dose for Phase I trials and thus,

one of ordinary skill in the art does not make a direct assumption of the MTD in humans from the MTD data obtained in mice. As further evidence, in Table 4 of Newell the comparative data for ratios of human maximum administered dose to rodent maximum administered/tolerated dose for 14 anticancer drugs under study are provided, confirming that there is a high variability between those two values. Thus, contrary to the argument presented in the Office Action, one of ordinary skill in the art does not make a direct extrapolation between these values.

In addition, with regards to the 200 mcg/kg (0.6 mg/m^2) toxicity level in the mouse model in Meco (page 134, left column, "In vivo studies"), Applicants note that the MTD in mice described in Meco does not correspond to that recited in van Kesteren. Meco discloses that in the mice model, a dose of 0.2 mg/kg (0.6 mg/m^2) of ET-743 as single agent "displayed toxicity", thus 0.1 mg/kg (0.3 mg/m^2) was identified as the MTD and was the dose chosen for ET-743 to be combined with doxorubicin. On the other hand, van Kesteren (page 4726, left column, lines 22-25) recites that the LD_{10} (MTD) in mice was of 0.2 mg/kg (0.6 mg/m^2). Accordingly, a variability of 50% exists between the disclosures in these two documents, which shows a highly uncertainty level. The current claims recite a dosage of ET-743 between 0.6 and 0.75 mg/m^2 which in comparison is clearly a narrow range.

Moreover, the dosages taught in Meco do not correspond to the dosage regimen for the combination of between 0.6 and 0.75 mg/m^2 for ET-743 in combination with about 50 mg/m^2 or about 60 mg/m^2 of doxorubicin, as claimed in claim 1. Meco discloses that the *in vivo* assays of the combination of ET-743 and doxorubicin are carried out at the doses of 0.1 mg/kg and 10 mg/kg, respectively (Meco, page 134, left column, "In vivo studies"). However, the representative surface area to weight ratio differs depending on the species, and the factor generally used in mice to convert dosages expressed as mg/kg to mg/m^2 is 3. Thus, a dosage of

0.1 mg/kg of ET-743 corresponds to 0.3 mg/m^2 and a dosage of 10 mg/kg of doxorubicin corresponds to 30 mg/m^2. Accordingly, the dosages taught in Meco are below those currently claimed where the instantly claimed dosages have shown antitumor activity with the avoidance of intolerable side effects.

Unexpected Results

Applicants have provided evidence that the claimed methods result in anti-tumor activity without dose-limiting toxicity. The results are surprising when considered in the context of the field as a whole, particularly because the literature at the time of filing provides several examples of combinations with doxorubicin resulting in undesired toxicity. For example, the Dorr reference (cited in the Office Action) describes drug interactions between interferon alpha and doxorubicin where substantial reductions of the amount of doxorubicin are required despite prior *in vitro* and *in vivo* data showing that the combination had antitumor activity, as described in Sarosy et al. (Cancer Research, vol.46, 5368-5371, 1986). Additional examples are found in the cardiotoxic effects of anthracycline-taxane combinations as described in Perotti et al., or the combination of trastuzumab with doxorubicin/cyclophosphamide as discussed in Chabner et al., which demonstrated an "unacceptable rate of cardiotoxicity".

Applicants have surprisingly found a combination of dosages which results in antitumor activity while avoiding intolerable toxicities. Specifically, when administered in combination as claimed, ET-743 has shown antitumor activity at a dose much lower than that recommended in the van Kesteren reference cited in the Office Action. Van Kesteren provides a clear recommendation that a dose of 1500 micrograms/m^2 ET-743 should be administered to achieve anti-tumor activity (see Abstract, last line). Similarly, a recommended dose level of 1500

micrograms/m^2 ET-743 for 24 h infusions or 1650 micrograms/m^2 ET-743 for 3 h infusions is taught in Bowman.

In view of the prior art cited by the Examiner it would not be obvious that a dose range of 0.6 to 0.75 mg/m^2 for ET-743 in combination with a dose of about 50 mg/m^2 or about 60 mg/m^2 for doxorubicin results in antitumor activity while avoiding intolerable toxicities.

Provisional Obviousness-Type Double-Patenting

Claims 1 and 3-9 are provisionally rejected for obviousness-type double patenting over claims 1-11 and 19-20 of US 11/577,790.

Applicants respectfully traverse. However, because the rejections are provisional, Applicants respectfully request that the rejections be held in abeyance pending the determination of patentable subject matter. Applicants suggest that if all other rejections are overcome, it is appropriate to withdraw the provisional double-patenting rejections and allow the instant application to issue, as directed by the MPEP:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. (MPEP §804).

Applicants reserve the right to provide arguments against the provisional rejection at a later time, if necessary.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this response to Deposit Account No. **50-3732**, Order No. 13566.105020. In the event that an extension of time is required, or which may be required in

addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13566.105020.

Respectfully submitted,
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